This policy refers to Stelara (ustekinumab) injection. Stelara (ustekinumab) for self-administered subcutaneous injection is obtained under the pharmacy benefit.

Stelara is proven and/or medically necessary for the treatment of:

**Crohn’s disease when ALL of the following criteria are met:**
- Diagnosis of moderately to severely active Crohn’s disease; and
- One of the following:
  - For **initial therapy**, all of the following:
    - Stelara is to be administered as a single intravenous induction dose; and
    - Stelara induction dosing is in accordance with the United States Food and Drug Administration approved labeled dosing for Crohn’s disease:
      - 260mg for patients weighing ≤55kg
      - 390mg for patients weighing >55kg to ≤85kg
      - 520mg for patients weighing >85kg
    - Patient is not receiving Stelara in combination with either of the following:
      - Biologic DMARD [e.g., infliximab, Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
      - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]
    - Authorization will be for one induction dose.
  - For **continuation of therapy**, all of the following:
    - Documentation of positive clinical response; and
    - Physician attestation that the patient or caregiver is not competent to administer Stelara FDA labeled for self-administration; physician must submit explanation; and
    - Stelara is to be subcutaneously administered 8 weeks after the initial intravenous dose; and
    - Stelara continuation dosing is in accordance with the United States Food and Drug Administration approved labeled dosing for Crohn’s disease: 90mg every 8 weeks subcutaneously; and
    - Patient is not receiving Stelara in combination with either of the following:
      - Biologic DMARD [e.g., infliximab, Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
      - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]
    - Authorization for no more than 12 months.

**Plaque psoriasis when ALL of the following criteria are met:**
- For **initial therapy**, all of the following:

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**Related Commercial Policies**
- Maximum Dosage
- Provider Administered Drugs – Site of Care
- Self-Administered Medications

**Community Plan Policy**
- Stelara® (Ustekinumab)
- Diagnosis of moderate to severe plaque psoriasis; and
- Patient is a candidate for systemic therapy; and
- Physicianattestation that the patient or caregiver is not competent to administer Stelara FDA labeled for self-administration; physician must submit explanation; and
- Stelara is initiated and titrated according to US Food and Drug Administration labeled dosing for plaque psoriasis up to a maximum of (or equivalent dose and interval schedule):
  - 45mg every 12 weeks for patients weighing ≤100kg subcutaneously
  - 90mg every 12 weeks for patients weighing >100kg subcutaneously

- Patient is not receiving Stelara in combination with any of the following:
  - Biologic DMARD [e.g., Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
  - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]
  - Phosphodiesterase 4 (PDE4) inhibitor [e.g., Otezla (apremilast)]

- Initial authorization is for no more than 12 months.

**For continuation of therapy, all** of the following:
- Documentation of positive clinical response; and
- Physician attestation that the patient or caregiver is not competent to administer Stelara FDA labeled for self-administration; physician must submit explanation; and
- Stelara is initiated and titrated according to US Food and Drug Administration labeled dosing for plaque psoriasis up to a maximum of (or equivalent dose and interval schedule):
  - 45mg every 12 weeks for patients weighing ≤100kg subcutaneously
  - 90mg every 12 weeks for patients weighing >100kg subcutaneously

- Patient is not receiving Stelara in combination with any of the following:
  - Biologic DMARD [e.g., infliximab, Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
  - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]
  - Phosphodiesterase 4 (PDE4) inhibitor [e.g., Otezla (apremilast)]

- Authorization is for no more than 12 months.

**Psoriatic arthritis when ALL of the following criteria are met:**

- For initial therapy, all of the following:
  - Diagnosis of psoriatic arthritis; and
  - Stelara is initiated and titrated according to US Food and Drug Administration labeled dosing for psoriatic arthritis up to a maximum of 90mg every 12 weeks subcutaneously (or equivalent dose and interval schedule); and
  - Physician attestation that the patient or caregiver is not competent to administer Stelara FDA labeled for self-administration; physician must submit explanation; and
  - Patient is not receiving Stelara in combination with any of the following:
    - Biologic DMARD [e.g., Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
    - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]
    - Phosphodiesterase 4 (PDE4) inhibitor [e.g., Otezla (apremilast)]

  - Initial authorization is for no more than 12 months.

- For continuation of therapy, all of the following:
  - Documentation of positive clinical response; and
  - Physician attestation that the patient or caregiver is not competent to administer Stelara FDA labeled for self-administration; physician must submit explanation; and
  - Stelara is initiated and titrated according to US Food and Drug Administration labeled dosing for psoriatic arthritis up to a maximum of 90mg every 12 weeks subcutaneously (or equivalent dose and interval schedule); and
  - Patient is not receiving Stelara in combination with any of the following:
    - Biologic DMARD [e.g., infliximab, Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
    - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]
    - Phosphodiesterase 4 (PDE4) inhibitor [e.g., Otezla (apremilast)]

  - Authorization is for no more than 12 months.

**Ulcerative colitis when ALL of the following criteria are met:**

- Diagnosis of moderately to severely active ulcerative colitis; and
- One of the following:
  - For initial therapy, all of the following:
    - Stelara is to be administered as a single intravenous induction dose; and
- Stelara induction dosing is in accordance with the United States Food and Drug Administration approved labeled dosing for ulcerative colitis:
  - 260mg for patients weighing ≤55kg
  - 390mg for patients weighing >55kg to ≤85kg
  - 520mg for patients weighing >85kg

    **and**

- Patient is not receiving Stelara in combination with either of the following:
  - Biologic DMARD [e.g., infliximab, Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
  - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]\(^{16}\)

    **and**

- Authorization will be for one induction dose.
  - For **continuation of therapy**, all of the following:
    - Documentation of positive clinical response; and
    - Physician attestation that the patient or caregiver is not competent to administer Stelara FDA labeled for self-administration; and
    - Stelara is to be subcutaneously administered 8 weeks after the initial intravenous dose; and
    - Stelara continuation dosing is in accordance with the United States Food and Drug Administration approved labeled dosing for ulcerative colitis: 90mg every 8 weeks subcutaneously; and
    - Patient is not receiving Stelara in combination with either of the following:
      - Biologic DMARD [e.g., infliximab, Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
      - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]\(^{16}\)

    **and**

- Authorization is for no more than 12 months.

**Stelara is unproven and not medically necessary for the treatment of multiple sclerosis.**

In available studies, Stelara does not demonstrate efficacy in the treatment of multiple sclerosis.

**APPLICABLE CODES**

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

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<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
</tr>
</thead>
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<tr>
<td>J3357</td>
<td>Ustekinumab, for subcutaneous injection, 1 mg</td>
</tr>
<tr>
<td>J3358</td>
<td>Ustekinumab for intravenous injection, 1 mg</td>
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<table>
<thead>
<tr>
<th>ICD-10 Diagnosis Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>K50.00</td>
<td>Crohn's disease of small intestine without complications</td>
</tr>
<tr>
<td>K50.011</td>
<td>Crohn's disease of small intestine with rectal bleeding</td>
</tr>
<tr>
<td>K50.012</td>
<td>Crohn's disease of small intestine with intestinal obstruction</td>
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<tr>
<td>K50.80</td>
<td>Crohn's disease of both small and large intestine without complications</td>
</tr>
<tr>
<td>K50.811</td>
<td>Crohn's disease of both small and large intestine with rectal bleeding</td>
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<td>ICD-10 Diagnosis Code</td>
<td>Description</td>
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<td>-------------</td>
</tr>
<tr>
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<td>Crohn's disease, unspecified, with unspecified complications</td>
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<td>K51.012</td>
<td>Ulcerative (chronic) pancolitis with intestinal obstruction</td>
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<td>K51.018</td>
<td>Ulcerative (chronic) pancolitis with other complication</td>
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<td>K51.50</td>
<td>Left sided colitis without complications</td>
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<td>K51.511</td>
<td>Left sided colitis with rectal bleeding</td>
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<td>K51.80</td>
<td>Other ulcerative colitis without complications</td>
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<td>K51.811</td>
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<td>Other ulcerative colitis with intestinal obstruction</td>
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<td>K51.814</td>
<td>Other ulcerative colitis with abscess</td>
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<td>K51.818</td>
<td>Other ulcerative colitis with other complication</td>
</tr>
<tr>
<td>K51.819</td>
<td>Other ulcerative colitis with unspecified complications</td>
</tr>
</tbody>
</table>
ICD-10 Diagnosis Code | Description
--- | ---
K51.90 | Ulcerative colitis, unspecified, without complications
K51.911 | Ulcerative colitis, unspecified with rectal bleeding
K51.912 | Ulcerative colitis, unspecified with intestinal obstruction
K51.913 | Ulcerative colitis, unspecified with fistula
K51.914 | Ulcerative colitis, unspecified with abscess
K51.918 | Ulcerative colitis, unspecified with other complication
K51.919 | Ulcerative colitis, unspecified with unspecified complications
K51.40 | Inflammatory polyps of colon without complications
K51.411 | Inflammatory polyps of colon with rectal bleeding
K51.412 | Inflammatory polyps of colon with intestinal obstruction
K51.413 | Inflammatory polyps of colon with fistula
K51.414 | Inflammatory polyps of colon with abscess
K51.418 | Inflammatory polyps of colon with other complication
K51.419 | Inflammatory polyps of colon with unspecified complications
L40.0 | Psoriasis vulgaris
L40.1 | Generalized pustular psoriasis
L40.2 | Acrodermatitis continua
L40.3 | Pustulosis palmaris et plantaris
L40.4 | Guttate psoriasis
L40.50 | Arthropathic psoriasis, unspecified
L40.51 | Distal interphalangeal psoriatic arthropathy
L40.52 | Psoriatic arthritis mutilans
L40.53 | Psoriatic spondylitis
L40.54 | Psoriatic juvenile arthropathy
L40.59 | Other psoriatic arthropathy
L40.8 | Other psoriasis
L40.9 | Psoriasis, unspecified

**Maximum Dosage Requirements**

**Maximum Allowed Quantities by HCPCS Units**

This section provides information about the maximum dosage per administration for ustekinumab administered by a medical professional.

<table>
<thead>
<tr>
<th>Medication Name</th>
<th>Maximum Dosage per Administration</th>
<th>HCPCS Code</th>
<th>Maximum Allowed</th>
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<tr>
<td>Brand</td>
<td>Generic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stelara</td>
<td>ustekinumab</td>
<td>90 mg</td>
<td>J3357</td>
</tr>
<tr>
<td></td>
<td></td>
<td>520 mg</td>
<td>J3358</td>
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</table>

**Maximum Allowed Quantities by National Drug Code (NDC) Units**

The allowed quantities in this section are calculated based upon both the maximum dosage information supplied within this policy as well as the process by which NDC claims are billed. This list may not be inclusive of all available NDCs for each drug product and is subject to change.

<table>
<thead>
<tr>
<th>Medication Name</th>
<th>How Supplied</th>
<th>National Drug Code</th>
<th>Maximum Allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand</td>
<td>Generic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stelara</td>
<td>ustekinumab</td>
<td>45 mg/0.5 mL prefilled syringe</td>
<td>57894-0060-03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45 mg/0.5 mL solution in vials</td>
<td>57894-0060-02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90 mg/1 mL prefilled syringe</td>
<td>57894-0061-03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>130 mg/26 mL solution in vials</td>
<td>57894-0054-27</td>
</tr>
</tbody>
</table>
BACKGROUND

Stelara is a human IgG1κ monoclonal antibody that binds with high affinity and specificity to the p40 protein subunit used by both the interleukin (IL)-12 and IL-23 naturally occurring cytokines. IL-12 and IL-23 are involved in inflammatory and immune responses, such as natural killer cell activation and CD4+ T-cell differentiation and activation.1

BENEFIT CONSIDERATIONS

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

CLINICAL EVIDENCE

Proven

**Ulcerative Colitis**

Ustekinumab was evaluated in two randomized, double-blind, placebo-controlled clinical studies in adult patients with moderately to severely active ulcerative colitis who had an inadequate response to or failed to tolerate a biologic (i.e., TNF blocker and/or vedolizumab), corticosteroids, and/or immunomodulator therapy. The 8-week intravenous induction study was followed by the 44-week subcutaneous randomized withdrawal maintenance study for a total of 52 weeks of therapy.1,21

A total of 961 patients were randomized at Week 0 to a single intravenous administration of ustekinumab of approximately 6 mg/kg, 130 mg (a lower dose than recommended), or placebo. Patients (523 patients) who had a response to induction therapy 8 weeks after administration of intravenous ustekinumab were randomly assigned again to receive subcutaneous maintenance injections of 90 mg of ustekinumab (either every 12 weeks [172 patients] or every 8 weeks [176]) or placebo (175) for 44 weeks. The primary end point in the induction trial (week 8) and the maintenance trial (week 44) was clinical remission (defined as a total score of ≤2 on the Mayo scale [range, 0 to 12, with higher scores indicating more severe disease] and no subscore >1 [range, 0 to 3] on any of the four Mayo scale components). The percentage of patients who had clinical remission at week 8 among patients who received intravenous ustekinumab at a dose of 130 mg (15.6%) or 6 mg per kilogram (15.5%) was significantly higher than that among patients who received placebo (5.3%) (P<0.001 for both comparisons). Among patients who had a response to induction therapy with ustekinumab and underwent a second randomization, the percentage of patients who had clinical remission at week 44 was significantly higher among patients assigned to 90 mg of subcutaneous ustekinumab every 12 weeks (38.4%) or every 8 weeks (43.8%) than among those assigned to placebo (24.0%) (P = 0.002 and P<0.001, respectively). The incidence of serious adverse events with ustekinumab was similar to that with placebo. The proportion of patients achieving histologic-endoscopic mucosal improvement during maintenance treatment was 75/172 (44%) among patients on ustekinumab and 40/172 (23%) in patients on placebo at Week 44. The relationship of histologic-endoscopic mucosal improvement at Week 44 to progression of disease or long-term outcomes was not evaluated. At Week 44, endoscopic normalization was achieved in 51/176 (29%) of patients treated with ustekinumab and in 32/175 (18%) of patients in placebo group. The authors concluded that ustekinumab was more effective than placebo for inducing and maintaining remission in patients with moderate-to-severe ulcerative colitis.1,21

**Crohn’s Disease**

Ustekinumab was evaluated in three randomized, double-blind, placebo-controlled clinical studies in adult patients with moderately to severely active Crohn’s disease. There were two 8-week intravenous induction studies followed by a 44-week subcutaneous randomized withdrawal maintenance study representing 52 weeks of therapy.1,17

In the two induction studies, 1409 patients were randomized, and 1368 (CD-1, n=741; CD-2, n=628) were included in the final efficacy analysis. Induction of clinical response at Week 6 and clinical remission at Week 8 were primary endpoints. In both studies, patients were randomized to receive a single intravenous administration of ustekinumab at approximately 6 mg/kg, placebo, or 130 mg. In the first study, patients had failed or were intolerant to prior treatment with a TNF blocker: 29% patients had an inadequate initial response (primary non-responders), 69% responded but subsequently lost response (secondary non-responders) and 36% were intolerant to a TNF blocker. Of these patients, 48% failed or were intolerant to one TNF blocker and 52% had failed 2 or 3 prior TNF blockers. At baseline and throughout this study, approximately 46% of the patients were receiving corticosteroids and 31% of the
patients were receiving immunomodulators (azathioprine, 6-mercaptopurine, methotrexate). The median baseline CDAI score was 319 in the ustekinumab approximately 6 mg/kg group and 313 in the placebo group.\textsuperscript{1,17,18}

In the second induction study, patients had failed or were intolerant to prior treatment with corticosteroids (81% of patients), at least one immunomodulator; (68% of patients), or both (49% of patients). Additionally, 69% never received a TNF blocker and 31% previously received but had not failed a TNF blocker. At baseline, and throughout the study, approximately 39% of the patients were receiving corticosteroids and 35% of the patients were receiving immunomodulators. The median baseline CDAI score was 286 in the ustekinumab and 290 in the placebo group.\textsuperscript{1,17,18}

In both of the induction studies, a greater proportion of patients treated with ustekinumab achieved clinical response at Week 6 and clinical remission at Week 8 compared to placebo. Clinical response and remission were significant as early as Week 3 in ustekinumab treated patients and continued to improve through Week 8.\textsuperscript{1,17,18}

The maintenance study, evaluated 388 patients who achieved clinical response (≥100 point reduction in CDAI score) at Week 8 of induction with ustekinumab in either of the induction studies. Patients were randomized to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks or placebo for 44 weeks.\textsuperscript{1,17,18}

At Week 44, 47% of patients who received ustekinumab were corticosteroid-free and in clinical remission, compared to 30% of patients in the placebo group. At Week 0 of this study, 34/56 (61%) ustekinumab treated patients who previously failed or were intolerant to TNF blocker therapies were in clinical remission and 23/56 (41%) of these patients were in clinical remission at Week 44. In the placebo arm, 27/61 (44%) patients were in clinical remission at Week 0 while 16/61 (26%) of these patients were in remission at Week 44. At Week 0 of this study, 46/72 (64%) ustekinumab treated patients who had previously failed immunomodulator therapy or corticosteroids (but not TNF blockers) were in clinical remission and 45/72 (63%) of these patients were in clinical remission at Week 44. In the placebo arm, 50/70 (71%) of these patients were in clinical remission at Week 0 while 31/70 (44%) were in remission at Week 44. In the subset of these patients who were also naïve to TNF blockers, 34/52 (65%) of ustekinumab treated patients were in clinical remission at Week 44 as compared to 25/51 (49%) in the placebo arm. Patients who were not in clinical response 8 weeks after ustekinumab induction were not included in the primary efficacy analyses; however, these patients were eligible to receive a 90 mg subcutaneous injection of ustekinumab upon entry into the maintenance study. Of these patients, 102/219 (47%) achieved clinical response eight weeks later and were followed for the duration of the study.\textsuperscript{1,17,18}

**Plaque Psoriasis**

A phase 3, multi-center, double-blind, placebo-controlled, randomized study evaluated the safety and efficacy of ustekinumab in patients age 12 to 17 years who had moderate-to-severe psoriasis.\textsuperscript{17} Patients (n = 110) were randomly assigned (2:2:1:1) ratio to ustekinumab (SD; 0.75 mg/kg [≤60 kg], 45 mg [>60 - ≤100 kg], and 90 mg [>100 kg]) or half-standard dosing (HSD; 0.375 mg/kg [≤60 kg], 22.5 mg [>60 - ≤100 kg], and 45 mg [>100 kg]) at weeks 0 and 4 and every 12 weeks or placebo at weeks 0 and 4 with crossover to ustekinumab SD or HSD at weeks 12 and 16 and thereafter every 12 weeks through week 40. At week 8, patients with a PASI increase ≥50% from baseline were eligible to commence treatment with moderate-to-high potency topical steroid preparations through week 12. The primary endpoint was the proportion of patients with a Physician’s Global Assessment (PGA) 0/1 at week 12. Major secondary endpoints were the proportions of patients achieving at least 75% improvement in PASI (PASI 75) and at least 90% improvement in PASI (PASI 90) at week 12 and the change from baseline in Children’s Dermatology Life Quality Index (CDLQI) at week 12. Assessments were performed through week 52. At week 12, the proportions of patients achieving PGA 0/1 were significantly greater in the HSD (67.6%) and SD (69.4%) groups versus placebo (5.4%; P < 0.001 for both dose groups). Approximately one-third of patients in each ustekinumab group achieved PGA 0/1 at week 4. Significantly greater proportions of patients in the HSD (32.4%) and SD (47.2%) groups achieved a PGA of 0 at week 12 compared to placebo (2.7%, but P < 0.001). Significantly greater proportions of patients receiving ustekinumab achieved PASI 75 (HSD, 78.4%; SD, 80.6%; placebo, 10.8%; P < 0.001) or PASI 90 (HSD, 54.1%; SD, 61.1%; placebo, 5.4%; P < 0.001). Additionally, 21.6% of patients in the HSD group and 38.9% in the SD group achieved a PASI score of 0 (cleared) at week 12 compared with 2.7% in the placebo group (P = .014 and P < 0.001, respectively). The treatment effect of both the HSD and SD of ustekinumab through week 12 for patients <60 kg was consistent with that observed in patients >60 kg to ≤100 kg. Placebo patients who crossed over to ustekinumab at week 12, PASI 75 response rates increased by week 16 and were maintained through week 52. The proportions of patients achieving PGA 0/1, PASI 75, or PASI 90 after crossover were generally similar to those observed in patients who started ustekinumab at baseline. Through week 40, all 110 patients received at least 1 injection of ustekinumab; among these, 81.8% reported an adverse event (AE) through week 60. By week 12, only one serious AE (SAE) was reported in the HSD group. After week 12, 5 additional singular SAEs were reported (total, 6; HSD, 5; SD, 1) through week 60. The investigators concluded that ustekinumab, in patients 12 to 17 years, the standard dose provided response comparable to that in adults with no unexpected adverse events through 1 year.
Griffiths et al. conducted a blinded, multi-center, head-to-head comparison of ustekinumab versus etanercept in the treatment of moderate-to-severe plaque psoriasis.\textsuperscript{11} Patients (n=903) were randomly assigned in a 3:5:5 ratio to receive subcutaneous injections of ustekinumab 45 mg (n=209) at weeks 0 and 4, ustekinumab 90 mg (n=347) at weeks 0 and 4, or etanercept 50 mg (n=347) twice weekly for 12 weeks. The primary end point was the proportion of patients with at least 75% improvement in the PASI index at week 12. A secondary end point was the proportion with cleared or minimal disease on the basis of the physician’s global assessment. At week 12, a total of 67.5% of patients who received 45 mg of ustekinumab and 73.8% of patients who received 90 mg of ustekinumab had at least 75% improvement in the PASI score, as compared with 56.8% of those who received high-dose etanercept (p=0.01 and p<0.001, respectively). Similarly, 65.1% of patients who received 45 mg of ustekinumab and 70.6% of patients who received 90 mg of ustekinumab had cleared or minimal disease according to the physician’s global assessment, as compared with 49.0% of those who received etanercept (p<0.001 for both comparisons). Among patients who did not have a response to etanercept, 48.9% had at least 75% improvement in the PASI within 12 weeks after crossover to ustekinumab. One or more adverse events occurred through week 12 in 66.0% of patients who received 45 mg of ustekinumab and 69.2% of patients who received 90 mg of ustekinumab and in 70.0% who received etanercept; 1.9%, 1.2%, and 1.2%, respectively, had serious adverse events. Safety patterns were similar before and after crossover from etanercept to ustekinumab. The investigators concluded that ustekinumab at a dose of 45 or 90 mg had superior efficacy to high-dose etanercept over a 12-week period in patients with psoriasis.

### Unproven

#### Multiple Sclerosis

Kasper et al. conducted a phase I, double-blind, placebo-controlled, sequential dose escalation study in 20 subjects with multiple sclerosis (MS).\textsuperscript{8} Subjects were randomized (4:1) to receive a single subcutaneous injection of either ustekinumab (0.3, 0.75, 1.5, and 3 mg/kg) or placebo. Clinical and laboratory evaluations were performed through 16 weeks following administration. Single subcutaneous administrations of ustekinumab in this first study of relapsing MS were generally well tolerated. Adverse events were generally mild or moderate, with no apparent dose-related trends. There was a large degree of variability in T2 lesion volume and total number of gadolinium-positive lesions, both unaffected by dose escalation. Three relapses of MS occurred in two placebo-treated subjects. Over the range of single doses studied, the median Tmax ranged from 9.0 to 16.5 days, and the median T1/2 ranged from 20.2 to 30.9 days. The authors concluded that safety of ustekinumab in MS needs to be tested in a study of longer duration and involving a larger cohort of subjects.

In a phase II, multicenter, randomized, double-blind, placebo-controlled trial, Segal et al. studied repeated injections of ustekinumab in patients (n=249) with relapsing-remitting multiple sclerosis (RRMS).\textsuperscript{9} Subjects aged 18-65 years were assigned to one of five groups: placebo (n=49) or four different ustekinumab dosages (n=50 for all) at weeks 0, 1, 2, 3, 7, 11, 15, and 19. Ustekinumab doses were 27 mg, 90 mg q8w, 90 mg, or 180 mg; the 90 mg q8w dosage group received placebo substitute at weeks 7 and 15. The primary endpoint was the cumulative number of new gadolinium-enhancing T1-weighted lesions on serial cranial MRI through week 23. Patients were followed up through week 37. In the intent to treat analysis, ustekinumab treatment did not show a significant reduction in the primary endpoint for any dosage groups versus placebo. At week 37, adverse events occurred in 38 (78%) placebo-treated patients and 170 (85%) ustekinumab-treated patients, with infections most commonly reported. Serious adverse events occurred in one (2%) placebo-treated patient and six (3%) ustekinumab-treated patients. Malignant diseases were reported in two patients shortly after the initiation of ustekinumab treatment; both patients were withdrawn from the trial and given appropriate treatment, which resulted in complete remission. No serious infections, cardiovascular events, or exacerbation of demyelinating events occurred. A dose-dependent increase in serum concentrations of ustekinumab was recorded. The investigators concluded that ustekinumab is generally well tolerated but does not show efficacy in reducing the cumulative number of gadolinium-enhancing T1-weighted lesions in multiple sclerosis.

### Professional Societies

#### American Academy of Dermatology

The American Academy of Dermatology guidelines of care for the management of psoriasis and psoriatic arthritis (PsA) state that patients with limited skin disease should not automatically be treated with systemic treatment if they do not improve, because treatment with systemic therapy may carry more risk than the disease itself.\textsuperscript{10}

The strength of AAD recommendations for the treatment of moderate to severe plaque psoriasis using ustekinumab is A (highest recommendation; level I evidence). Compared with the TNF-alfa inhibitors, the most comprehensive ustekinumab safety data to date come from a pooled analysis of phase II and phase III clinical trials involving slightly more than 3,000 patients with just over 3 years of continuous therapy. Therefore, the use of registries to monitor the long-term safety of ustekinumab and other new agents currently under development, and to monitor the long-term safety of all of the systemic agents available, is an essential step in defining the long-term adverse effects of ustekinumab and other new agents.\textsuperscript{11}
When considering the use of ustekinumab for PsA, the AAD states that until the results of ongoing phase III trials of ustekinumab for PsA become available, the TNF-alfa inhibitors should be considered the biologic class of choice for this patient population.\textsuperscript{11}

**Technology Assessments**

A 2016 Cochrane review was published to assess the efficacy and safety of anti-IL-12/23p40 antibodies for induction of remission in Crohn's disease. The review evaluated six studies with 2324 participants. The authors concluded that the high quality evidence suggests that ustekinumab is effective for induction of clinical remission and clinical improvement in patients with moderate to severe Crohn’s disease. Moderate to high quality evidence suggests that the optimal dosage of ustekinumab is 6 mg/kg. Briakinumab and ustekinumab appear to be safe. Moderate quality evidence suggests no increased risk of serious adverse events. Future studies are required to determine the long-term efficacy and safety of ustekinumab in patients with moderate to severe Crohn’s disease.\textsuperscript{19}

**U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Stelara is a human interleukin-12 and -23 antagonist indicated for the treatment of:\textsuperscript{1}

- Adult patients (18 years or older) with:
  - Moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
  - Active psoriatic arthritis, alone or in combination with methotrexate
  - Moderately to severely active Crohn’s disease
  - Moderately to severely active ulcerative colitis
- Adolescent patients (12 years or older) who are candidates for phototherapy or systemic therapy

**CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)**

Medicare does not have a National Coverage Determination (NCD) specifically for STELARA\textsuperscript{®} (ustekinumab). Local Coverage Determinations (LCDs)/ Local Coverage Articles (LCAs) exist; see the LCAs for Billing and Coding of Drug and Biological Infusions.

In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals. (Accessed January 24, 2019)

**REFERENCES**


### POLICY HISTORY/REVISION INFORMATION

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| 01/01/2020 | **Coverage Rationale**  
|            | Updated list of examples of janus kinase inhibitors; added Olumiant (baricitinib)  
|            | Revised coverage criteria for **Crohn’s disease**:  
|            | o One of the following:  
|            | - History of inadequate response or failure, contraindication, or intolerance to at least one tumor necrosis factor (TNF) blocker [e.g., infliximab, Humira (adalimumab), Cimzia (certolizumab)]; or  
|            | - Both of the following:  
|            | - History of inadequate response or failure, contraindication, or intolerance to at least one immunomodulator or corticosteroid (e.g., corticosteroids, 6-mercaptopurine, azathioprine, methotrexate, etc.); and  
|            | - Patient has never failed a TNF blocker [e.g., infliximab, Humira (adalimumab), Cimzia (certolizumab)]  
|            | o Patient is not receiving Stelara in combination with a phosphodiesterase 4 (PDE4) inhibitor [e.g., Otezla (apremilast)]  
|            | o Replaced criterion for **initial therapy** requiring "Stelara is to be administered as an intravenous induction dose" with "Stelara is to be administered as a single intravenous induction dose”  
|            | o Added criterion for **continuation of therapy** requiring documentation of positive clinical response [to Stelara]  
|            | Added coverage criteria for **ulcerative colitis**  
|            | Added ICD-10 diagnosis codes K51.00, K51.011, K51.012, K51.013, K51.014, |
**INSTRUCTIONS FOR USE**

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard benefit plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

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**Table: Updated maximum dosage requirements; added:**

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- Updated maximum dosage requirements; added:
  - **Maximum Allowed Quantities by HCPCS Units**
    - Maximum Dosage per Administration: 520 mg
    - HCPCS Code: J3358
    - Maximum Allowed: 520 HCPCS units (1 mg per unit)
  - **Maximum Allowed Quantities by National Drug Code (NDC) Units**
    - How Supplied: 130 mg/26 mL solution in vials
    - National Drug Code: 57894-0054-27
    - Maximum Allowed: 104 mL

**Supporting Information**

- Updated Clinical Evidence, FDA, and References sections to reflect the most current information
- Archived previous policy version 2019D00450